Quetiapine and Long-Term Weight Change: A Comprehensive Data Review of Patients With Schizophrenia

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Background: To assess the magnitude and pattern of weight change during long-term treatment with the atypical antipsychotic quetiapine.

Method: Data were collected from patients with a DSM-IV diagnosis of schizophrenia treated with quetiapine in the AstraZeneca clinical trials program from July 1993 to May 1999. Weight changes in patients treated for 12, 52, and 104 weeks were analyzed; the primary parameter was the change in weight at week 52.

Results: In total, 352 patients were treated with quetiapine for 52 weeks. The mean weight gain at this timepoint was 3.19 kg; median weight gain was 2.5 kg. Overall, 37% of patients gained ≥ 7% of their baseline body weight; however, the degree of weight gain was inversely related to baseline body mass index in this cohort. In patients treated with < 200 mg/day of quetiapine, mean weight gain was 1.54 kg, compared with 4.08 kg for 200 to 399 mg/day, 1.89 kg for 400 to 599 mg/day, and 3.57 kg for ≥ 600 mg/day; median weight gain was 0.95 kg, 3.40 kg, 2.00 kg, and 3.34 kg, respectively. Analysis of longitudinal weight changes indicated that most weight gain (> 60%) occurred within the first 12 weeks of quetiapine treatment, with modest changes after 6 months.

Conclusions: Long-term treatment with quetiapine monotherapy is associated with moderate weight gain. Most weight gain occurs within the first 12 weeks of treatment and has no clear dose relationship.

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Schizophrenia is a severe, debilitating condition with a prevalence rate of 4 to 7 per 1000 persons.[1] It is associated with a marked reduction in quality of life and ability to function, and the suicide rate is estimated to be 10% to 13%.[2] Although some patients do recover, the illness usually follows a chronic relapsing course, and the majority of patients require long-term antipsychotic treatment. Good, long-term tolerability is therefore essential, as side effects can have a negative impact on adherence, compromising treatment outcomes.[3]

The American Psychiatric Association recommends that atypical antipsychotics are used as first-line treatment for schizophrenia because of the decreased risk of extrapyramidal symptoms and tardive dyskinesia compared with conventional agents.[4] Within the atypical class, efficacy of the individual agents appears to be comparable.[5–8] However, their side effect profiles differ as a result of differences in their pharmacologic properties. One such side effect is potential weight gain, which occurs to varying degrees with the different atypical antipsychotics.

Weight gain can affect patients' quality of life, well-being, and vitality[9] and has been shown to reduce treatment adherence.[10,11] In a survey of 99 patients with schizophrenia, weight gain was second only to akinesia in terms of the distress caused by antipsychotic side effects.[12] Long-term weight gain is associated with obesity, dyslipidemia, hyperglycemia, and hypertension, which can, in turn, lead to increased cardiovascular and cerebrovascular

Table 1. Patient Demographics at Baseline (52-week cohort; N = 352)

Characteristic	Value
Male/female, %	73/27
Age, mean (SD), y	40 (12.2)
Weight, mean (SD), kg	77 (18.2)
Body mass index category at baseline (kg/m^2), N (%)[a]	
< 18.5	8 (2)
18.5 to < 25	128 (36)
25 to < 30	83 (24)
30 to < 35	28 (8)
≥ 35	17 (5)

[a]Height measurements were not available for 88 patients, and therefore their body mass index could not be calculated.

morbidity and mortality.[13,14] It is also a risk factor for the development of respiratory problems, osteoarthritis, type II diabetes, and various cancers.[13,14] The situation is further compounded by evidence that even in drug-naive or drug-free patients with schizophrenia, intra-abdominal fat levels and the prevalence of diabetes are higher than in the general population.[15,16] In addition, patients with mental illness have a high prevalence of cardiovascular risk factors, such as smoking, low exercise, and excess salt and alcohol intake. Compared with the general population, mortality rates are higher in patients with mental illness and in those with schizophrenia, and the leading cause of death in both groups is coronary heart disease.[17,18]

Among the atypical antipsychotics, long-term weight gain is recognized as a particular issue with clozapine and olanzapine.[19] In a retrospective chart review of patients treated with clozapine for up to 90 months, 70% had gained ≥ 10% of their baseline body weight at the end of the second year of treatment.[20] In a meta-analysis of 4 long-term studies with olanzapine involving almost 3000 patients, there was a weight gain of approximately 12 kg after 12 months of treatment at doses of 12.5 to 17.5 mg.[21]

The purpose of this analysis was to examine the AstraZeneca quetiapine clinical trials safety database to determine the magnitude and pattern of weight change in patients with schizophrenia treated with quetiapine, focusing on weight change at 52 weeks of treatment.

METHOD

Patients and Study Design

This study was a retrospective analysis of data from patients with a DSM-IV diagnosis of schizophrenia treated with quetiapine. Data were collected from all trials in the Seroquel Clinical Trials Database from July 1993 to May 1999, including controlled trials, open-label studies, and the corresponding open-label extension phases. Ethics approval was obtained for all studies, which were performed in accordance with the Declaration of Helsinki. All patients provided written, informed consent before entry into the studies.

Weight changes were analyzed in patients treated for 12 weeks (± 4 days), 52 weeks (± 30 days), and 104 weeks (± 45 days). To be eligible for inclusion in the analyses, patients had to have weight measurements recorded at baseline and at the relevant timepoints; i.e., an observed-cases approach was used to assess weight change. The primary cohort was the 52-week group. As patients in the 3 time cohorts are not directly comparable, additional analyses were carried out in 2 longitudinal cohorts to characterize the time course of weight change during the first and second years of quetiapine treatment. The first longitudinal cohort included patients with weight data recorded at 12 weeks (± 4 days), 26 weeks (± 14 days), and 52 weeks (± 30 days), and the second longitudinal cohort included patients with data recorded at 12 weeks (± 4 days), 52 weeks (± 30 days), and 104 weeks (± 45 days).

All concomitant medication was stopped before entry into the trials, but in some trials, concomitant antipsychotic medication was permitted during the open-label extension phases. Data were analyzed for all patients receiving quetiapine and for the subgroup of patients who received quetiapine monotherapy.

Data Analysis

Descriptive statistics are presented for the change in weight (kg) from baseline to final observation, stratified by baseline body mass index (BMI; kg/m^2) category and modal dose of quetiapine. The National Institutes of Health National Heart, Lung, and Blood Institute standard BMI categories were used for the analysis. Dose categories were < 200, 200–399, 400–599, and ≥ 600 mg/day. Confidence intervals (CIs) were calculated for the mean change in weight from baseline to last point of evaluation. Statistical significance was determined when 95% CI ranges did not cross zero.

The percentage of patients with clinically significant weight gain and weight loss was also assessed for all cohorts. The U.S. Food and Drug Administration (FDA) definition of clinically significant weight change, i.e., an increase or decrease of ≥ 7% of baseline body weight, was used.

RESULTS

Baseline Demography and Clinical Characteristics

Baseline demography and clinical characteristics of patients in the primary cohort (52 weeks) are shown in Table 1. Baseline characteristics of patients in the other cohorts were similar (data not shown).

Weight Change in the 12-Week Cohort

In total, 378 patients with schizophrenia had weight data available after treatment with quetiapine for 12 weeks; of these, 340 received quetiapine monotherapy.

Figure 1. Weight Change by Baseline Body Mass Index (BMI) Category in Patients With Schizophrenia Treated With Quetiapine for 12 Weeks

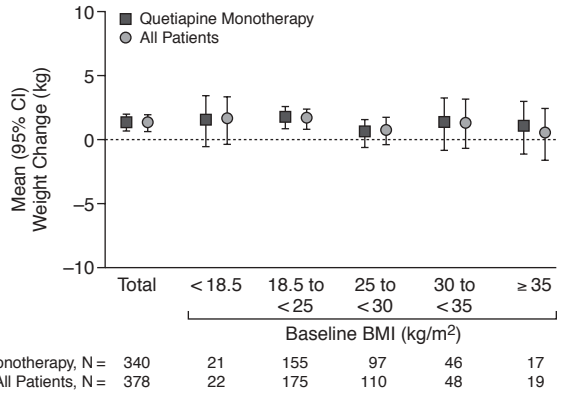


Figure 2. Weight Change by Modal Daily Dose of Quetiapine in Patients With Schizophrenia Treated for 12 Weeks

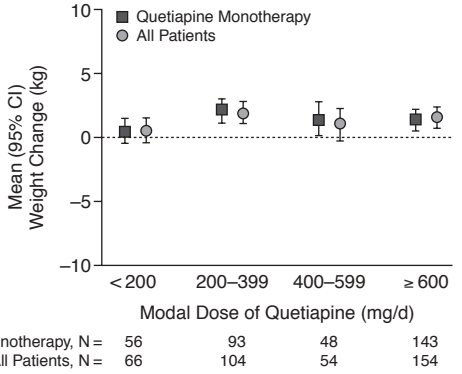


Table 2. Patients With Schizophrenia Who Lost or Gained ≥ 7% of Their Baseline Body Weight Following Treatment With Quetiapine, N (%)[a]

	≥ 7% Weight Loss			≥ 7% Weight Gain		
Group	12 Weeks	52 Weeks	104 Weeks	12 Weeks	52 Weeks	104 Weeks
Quetiapine monotherapy	27 (7.94)	39 (13.13)	15 (10.49)	61 (17.94)	115 (38.72)	68 (47.55)
All patients	30 (7.94)	45 (12.78)	19 (11.45)	66 (17.46)	131 (37.22)	75 (45.18)

[a]Data from the 3 cohorts are not directly comparable, as patients in each cohort did not necessarily have weight recorded at more than 1 (or 2) of the 3 timepoints.

Mean (95% CI) weight gain was 1.46 (0.98, 1.95) kg for all patients and 1.48 (0.98, 1.99) kg for the monotherapy group. Median weight gain was 1.15 kg for all patients and 1.36 kg for the monotherapy group.

Figure 1 shows the mean weight change stratified by baseline BMI category in both patient populations (all patients and patients receiving monotherapy). There was no significant weight gain in patients who were overweight or obese at baseline.

Figure 2 shows mean weight change stratified according to patients' modal daily dose of quetiapine. There was no relationship between quetiapine dose and weight change in either patient population.

The percentages of patients who gained or lost ≥ 7% of their baseline body weight are shown in Table 2.

Weight Change in the 52-Week Cohort

In total, 352 patients with schizophrenia had weight data available after treatment with quetiapine for 52 weeks; of these, 297 received quetiapine monotherapy. Mean (95% CI) weight gain was 3.19 (2.27, 4.11) kg for all patients and 3.59 (2.57, 4.61) kg for the monotherapy group. Median weight gain was 2.5 kg for all patients and 3.0 kg for the monotherapy group.

Figure 3 shows the mean weight change stratified by baseline BMI category in both patient populations (all patients and patients receiving monotherapy). Patients in the lower baseline BMI categories gained most weight. Evaluation of individual patient data from the monotherapy group indicated that in patients who were underweight at baseline (BMI < 18.5 kg/m^2), all had a normal BMI (18.5 to < 25 kg/m^2) at week 52 (data not shown).

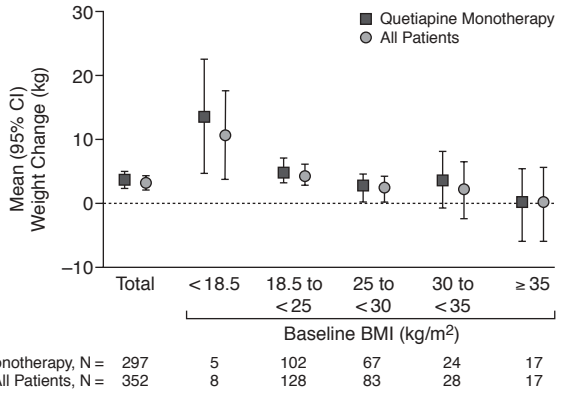
Figure 4 shows mean weight change stratified according to patients' modal daily dose of quetiapine. In patients treated with < 200 mg/day of quetiapine, mean weight gain was 1.54 kg, compared with 4.08 kg for 200 to 399 mg/day, 1.89 kg for 400 to 599 mg/day, and 3.57 kg for ≥ 600 mg/day; median weight gain was 0.95 kg, 3.40 kg, 2.00 kg, and 3.34 kg, respectively. There was no consistent relationship between quetiapine dose and weight change in either patient population.

The percentages of patients who gained or lost ≥ 7% of their baseline body weight are shown in Table 2.

Weight Change in the 104-Week Cohort

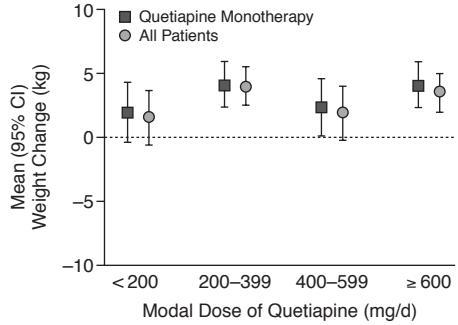
In total, 166 patients with schizophrenia had weight data available after treatment with quetiapine for 104 weeks; of these, 143 received quetiapine monotherapy. Mean (95% CI) weight gain was 5.16 (3.62, 6.70) kg for all patients and 5.59 (3.98, 7.20) kg for the monotherapy group. Median weight gain was 4.1 kg for all patients and 4.5 kg for the monotherapy group.

Figure 3. Weight Change by Baseline Body Mass Index (BMI) Category in Patients With Schizophrenia Treated With Quetiapine for 52 Weeks



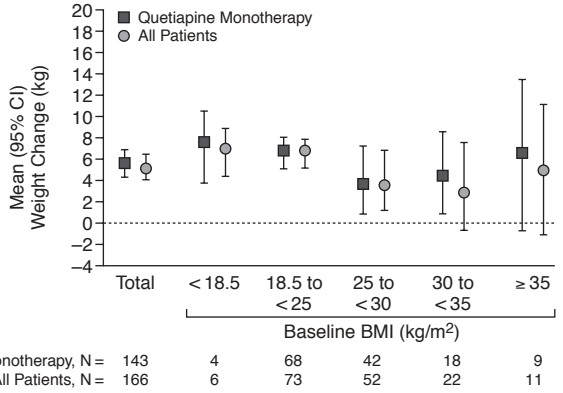
Monotherapy, N =	297	5	102	67	24	17
All Patients, N =	352	8	128	83	28	17

Figure 4. Weight Change by Modal Daily Dose of Quetiapine in Patients With Schizophrenia Treated for 52 Weeks



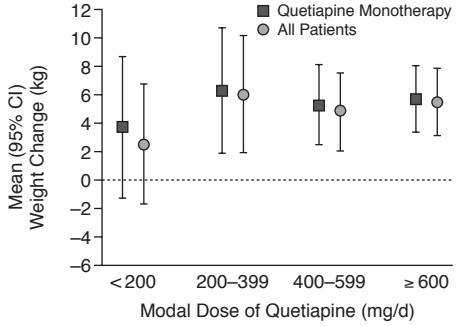
Monotherapy, N =	25	92	65	115
All Patients, N =	32	107	73	140

Figure 5. Weight Change by Baseline Body Mass Index (BMI) Category in Patients With Schizophrenia Treated With Quetiapine for 104 Weeks



Monotherapy, N =	143	4	68	42	18	9
All Patients, N =	166	6	73	52	22	11

Figure 6. Weight Change by Modal Daily Dose of Quetiapine in Patients With Schizophrenia Treated for 104 Weeks



Monotherapy, N =	10	30	46	57
All Patients, N =	13	33	51	69

Figure 5 shows the mean weight change stratified by baseline BMI category in both patient populations (all patients and patients receiving monotherapy). Evaluation of individual patient data from the monotherapy group indicated that in patients who were underweight at baseline (BMI < 18.5 kg/m^2), all had a BMI < 25 kg/m^2 at week 104 (data not shown).

Figure 6 shows mean weight change stratified according to patients' modal daily dose of quetiapine. There was no consistent relationship between quetiapine dose and mean weight change in either patient population.

The percentages of patients who gained or lost ≥ 7% of their baseline body weight are shown in Table 2.

Longitudinal Weight Change

Ninety-seven patients with schizophrenia had body weight data available at weeks 12, 26, and 52. These data indicate that during 1 year of treatment with quetiapine, 69% of the total mean weight gain occurred within the first 12 weeks, and 96% occurred in the first 26 weeks.

Similarly, data from the 12-52-104–week cohort (N = 50) indicated that 62% of the total weight gain occurred in the first 12 weeks of treatment. Furthermore, 99% of weight gain occurred in first year, with negligible weight change between 1 and 2 years.

DISCUSSION

Long-term weight gain is a potential issue with atypical antipsychotics. For most of these agents, weight changes over 6 and 12 months have been assessed and reported. However, with the exception of clozapine, there are few data available on weight gain with atypical antipsychotics beyond 1 year of treatment. The current

analysis provides information on the magnitude and pattern of weight change in patients with schizophrenia treated with quetiapine for up to 2 years. Data were assessed using an observed-cases approach; in contrast, most studies reported in the literature used last-observation-carried-forward methodology, which may underestimate the magnitude of weight gain with antipsychotics.[22]

The FDA defines clinically significant weight gain as an increase of ≥ 7% over baseline body weight, which is equivalent to approximately 5 kg in those with the average body weight of 70 kg. After 52 weeks of quetiapine treatment, mean weight gain was 3.19 kg and median weight gain was 2.50 kg. The corresponding values in patients treated for 104 weeks were 5.16 kg and 4.10 kg, respectively.

Data from the longitudinal cohorts in this analysis show that most weight gain with quetiapine (> 60%) occurs within the first 12 weeks of treatment. Furthermore, there was very little weight gain between 6 months and 1 year (4%; 12-26-52–week cohort) and between 1 and 2 years (1%; 12-52-104–week cohort).

In patients treated with quetiapine for 52 weeks, 37% gained ≥ 7% of their baseline body weight. However, patients' baseline body weight can have an effect on the degree of weight gain with atypical antipsychotics, with those who are underweight gaining the most weight. Indeed, in the 52-week cohort in the current study, patients in the lower baseline BMI categories gained most weight. Similar findings were reported in an earlier analysis of a smaller quetiapine dataset.[23] The trend in the 104-week cohort was less clear, but the data on weight gain by baseline BMI category were more variable for this cohort, possibly reflecting the small sample sizes, particularly in the BMI category > 35 kg/m^2. The sample size for the 104-week cohort is one of the limitations of the study, particularly in the BMI and dose analyses; nevertheless, the study provides important information on long-term weight change with quetiapine, at a timepoint for which there is very little information available for other atypical antipsychotics.

Another limitation of the current analysis is the lack of control group. However, the results of the current study are generally consistent with published comparative studies. In 1999, Allison et al.[24] carried out a meta-analysis to estimate weight change after 10 weeks of treatment with standard doses of clozapine, olanzapine, risperidone, and ziprasidone. Mean weight changes were 4.45 kg, 4.15 kg, 2.10 kg, and 0.04 kg, respectively, compared with an overall weight loss of 0.74 kg for placebo. In the current study, mean weight gain after 12 weeks of treatment with quetiapine was 1.46 kg.

More recently, 3 long-term comparative studies have been carried out, allowing assessment of the effects of the various atypical agents on long-term body weight. In the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) study, which was funded by the National Institute of Mental Health, 1493 patients with chronic schizophrenia were treated with olanzapine, risperidone, quetiapine, ziprasidone, or perphenazine for up to 18 months.[25] Overall weight gain, weight gain per month, and the percentage of patients who gained > 7% of their baseline body weight were greatest in the olanzapine group. Mean weight gain was 4.3 kg in the olanzapine group, compared with 0.36 kg for risperidone, 0.50 kg for quetiapine, –0.73 kg for ziprasidone, and –0.91 kg for perphenazine ($p < .001$). These results are generally consistent with the 12-month interim results of the Intercontinental Schizophrenia Outpatient Health Outcomes study,[26] a prospective, observational study in which almost 5000 patients with schizophrenia are being treated with quetiapine, olanzapine, risperidone, or haloperidol monotherapy for 3 years. Weight gain at 12 months was greater with olanzapine (3.4 kg) compared with risperidone (2.2 kg), haloperidol (2.2 kg), and quetiapine (1.9 kg). In addition, the odds ratio of gaining ≥ 7% of baseline body weight was significantly greater for olanzapine compared with the other antipsychotics. Finally, in the Comparison of Atypicals in First-Episode Psychosis study, which was a 52-week, randomized, double-blind study in first-episode psychosis, the percentages of patients who gained more than 7% of their baseline body weight were 80% for olanzapine, 57.6% for risperidone, and 50% for quetiapine.[27] The degree of weight gain in this study was greater than that observed in other long-term studies and is consistent with the observation that first-episode patients are more likely to exhibit weight gain with antipsychotic treatment.[28]

These results are generally consistent with the results of individual studies, in which the most weight gain was observed in patients receiving clozapine and olanzapine.[15,29,30] In prospective studies in which patients were treated with clozapine for 1 year, 60% to 70% of patients gained ≥ 10% of their baseline body weight.[31,32] Similar results were obtained in a retrospective chart review of patients treated with long-term clozapine.[20] During long-term treatment with olanzapine (median duration = 34 weeks), the mean weight gain was 5.6 kg, and 56% of patients gained ≥ 7% of their baseline body weight.[33] However, mean weight increases of 12 kg have been reported after 12 months of treatment with olanzapine doses of 12.5 to 17.5 mg.[21] Fewer data are available for risperidone, but prospective studies with risperidone indicate that it is associated with weight gain of approximately 2 kg after 1 year of treatment.[34,35]

As well as the magnitude, the time course of weight gain varies between atypical antipsychotics. The results of the current analysis show that for quetiapine, most weight gain occurs within the first 12 weeks of treatment, and there is very little change in weight beyond 6 months. Similarly, weight gain with risperidone appears to plateau after approximately 10 weeks.[19] In contrast, patients

treated with clozapine continued to gain weight during their third year of treatment.[20] In patients treated with olanzapine 5 to 20 mg/day, there was a trend toward a plateau after 39 weeks of treatment[36]; however, in those treated with doses of 12.5 to 17.5 mg, there was no indication of weight stabilization after 1 year of treatment.[21] In addition, weight increases with olanzapine appear to be dose-dependent.[21] In contrast, the results of the current study do not suggest that this is the case with quetiapine. Although the broad confidence intervals limit firm conclusions, the degree of weight gain associated with doses of quetiapine > 600 mg/day was generally similar to that observed with doses > 200 mg/day. This is an important observation, as the target dose of quetiapine for most patients with schizophrenia is 600 mg/day.

There are fewer long-term data available for the newer atypical antipsychotics ziprasidone and aripiprazole. The prescribing information for these products indicates that overall, they are weight neutral during long-term treatment,[37,38] although weight gain has been observed in some patients taking these agents.[39]

Mean weight change following long-term treatment with ziprasidone was 0.0 kg for those with a normal baseline BMI, compared with 1.4 kg and –1.3 kg for those with low and high baseline BMIs, respectively.[37] In a 52-week, double-blind, placebo-controlled study, overall weight change in patients treated with ziprasidone (approximately –3.0 kg) was similar to that observed with placebo (–3.6 kg).[40] However, it has been suggested that this weight loss may be due to the withdrawal of other atypical antipsychotics.[39] In the CATIE study, patients treated with ziprasidone lost 0.73 kg.[25]

Pooled analysis of data from two 52-week, randomized, double-blind studies with aripiprazole indicated a mean weight gain of 1.05 kg.[41] The percentage of patients with ≥ 7% weight gain after 1 year of treatment was 30% for patients with a baseline BMI of < 23 kg/m^2, 19% for those with a baseline BMI of 23 to 27 kg/m^2, and 8% for those with a baseline BMI of > 27 kg/m^2.[38] Comparison of the aripiprazole data with those of the other atypical antipsychotics should be made with caution, as the trial designs and patient populations were not necessarily well matched; this is important because many factors, such as gender and age, can influence changes in body weight.

The mechanism of action of weight gain observed during antipsychotic treatment is not fully understood. It is likely to be multifactorial, as numerous neurotransmitters, hormones, and neuropeptides are involved in the control of appetite and metabolism.[39] It has been suggested that the interaction of atypical antipsychotics with serotonergic and histaminergic receptors may play a role.

The long-term impact of weight gain associated with antipsychotic usage on glucose and lipid levels has not been extensively studied. However, a comprehensive literature review, which confirmed the differential changes in body weight during treatment with atypical antipsychotics, also indicated that increased adiposity in patients with schizophrenia can be associated with decreased insulin sensitivity, which may contribute to hyperglycemia and dyslipidemia.[42] These findings were considered in a more recent review, which postulates that the different weight gain observed among the atypical agents may correspond to differential changes in glucose and lipid levels.[43]

CONCLUSIONS

In this analysis, long-term treatment with quetiapine monotherapy was associated with moderate weight gain in patients with schizophrenia. Most weight gain with quetiapine occurred within the first 12 weeks of treatment and had no clear dose relationship. The choice of atypical antipsychotic treatment for patients with schizophrenia should be based on a careful risk-benefit analysis. As there is limited evidence of differences in efficacy between individual agents, tolerability is a key issue, particularly during long-term treatment. Weight gain, with its potential for reducing adherence and increasing morbidity, is one of a number of important side effects that should be considered when making treatment decisions for these patients.

Drug names: aripiprazole (Abilify), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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